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10/586,406

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EXAMINER

STOICA, ELLY GERALD

ART UNIT

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/586,406	Applicant(s) OKABE ET AL.	
	Examiner ELLY-GERALD STOICA	Art Unit 1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 06 August 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-21 is/are pending in the application.
- 4a) Of the above claim(s) 7-9 and 17-21 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-6, 10-16 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>10/19/2007;10/24/2007;10/31/2007</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of claims 1-6, 14 (in part) and 16 (in part) drawn to a substance, having an ability to bind to a CD61 protein and an inhibitory effect on inflammatory cytokine production in the reply filed on 08/06/2008 is acknowledged. The Examiner has opted to rejoin the Invention of Group III with the Group I since the searches made during the examination included the search for anti CD-61 antibodies.

Status of the claims

2. Claims 1-21 are pending. Claims 7-9, and 17-21 are withdrawn as being drawn to non- elected Inventions. Claims 1-6 and 10-16 are currently examined

..

Specification

3. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

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art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-6, and 10-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a substance, or a derivative thereof, having an ability to bind to a CD61 protein and an inhibitory effect on inflammatory cytokine production. The substance may be an antibody or another protein. The heavy chain antibody may have a polypeptide with SEQ ID NO: 4 and a light chain of SEQ ID NO: 8 and comprising a number of undisclosed deletions, substitutions or additions to the respective SEQ IDs. The antibody is also claimed as having at least one CDR (either of the heavy chain or light chain) (SEQ ID NOs 1-3 or 5-7) and comprising a number of undisclosed deletions, substitutions or additions to the respective SEQ IDs. The inflammatory cytokine may be any one of IFN- γ , TNF α , IL-1, and IL-6 and may also have an IL-10 production-inducing effect. The substance may be comprised in a pharmaceutical composition to be used in a method of inhibiting inflammatory cytokine production.

The rejection includes two issues which will be treated separately: one is the description of the substances claimed and the second one relates to the description of the antibodies *per se*.

With regard to the first issue, the description of the substances claimed, the specification discloses the substances as deoxyribonucleic acids, ribonucleic acids,

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proteins, peptides, and low-molecular substances. Examples of derivatives of the substances include prodrugs of the substances of the present invention. Such prodrugs are substances for which the derivative itself has no CD61 protein-binding ability and/or no inflammatory cytokine production-inhibitory effect, but which become substances exhibiting a CD61 protein-binding ability and an inflammatory cytokine production-inhibitory effect after administration into the body (p. 8, lines 8-9; p.16, lines 16-24). Thus, the claims are drawn to a genus of substances that is defined only by functionality only without any indication of a structural determinant of this functionality. The only structure disclosed is the antibody #33 for which the sequences of the variable heavy and light chains as well as the sequences of all CDRs are presented (p. 9 line 9 to p. 10 line 14).

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a desired functionality of an unnamed substance. There is not even identification of any particular portion of the structure that must be linked to the functional effect claimed (except of course the Ab#33). Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. Additionally, the description of one antibody (Ab #33)

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is not adequate written description of an entire genus of functionally equivalent polynucleotides and polypeptides or small molecules, which incorporate all variants and fragments claimed.

With regard to the second aspect, the description of the antibodies per se, as presented supra, the only description is for the antibody Ab#33. However, the claims are drawn to antibodies that are either described by one CDR only (claims 11 or 13) or by heavy or light chains and comprising a number of undisclosed deletions, substitutions or additions to the respective SEQ IDs without any indications which are the residues that are necessary for the functionality of the antibody and which are invariable. Thus, the claims are drawn to a genus of antibodies that is defined only by functionality only without any indication of a structural determinant of this functionality (with the exception of the Antibody #33).

Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. This is because the art, at the time that the invention was made, does not show that a CDR3 is universally solely responsible for antigen binding. The prior art does not show screening for antibodies by just defining CDR3. The methods rely on using an entire V_H or V_L and screening random complimentary chains. The prior art does not support a definition of an antibody structure solely by defining the CDR3 sequence of a V_H or V_L antigen (Klimka et al., British Journal of Cancer 83: 252-260,

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2000; Beiboer et al., J. Mol. Biol. 296:833, 2000; MacCallum et al., J. Mol. Biol. 262: 732-745, 1996).

Additionally, the description of one antibody (Ab #33) is not adequate written description of an entire genus of functionally equivalent polypeptides which incorporate all variants and fragments claimed.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that “applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the ‘written description’ inquiry, *whatever is now claimed*” (See page 1117). The specification does not “clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed” (See *Vas-Cath* at page 1116).

With the exception of the sequences referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides or proteins, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to

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be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only the antibody #33 but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

6. Claims 1-6, and 10-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an anti CD-61 antibody, does not reasonably provide enablement for any other substance, or a derivative thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731,737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

As presented *supra*, the claims are drawn to a substance, or a derivative thereof, having an ability to bind to a CD61 protein and an inhibitory effect on inflammatory

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cytokine production. The substance may be an antibody or another protein. The heavy chain antibody may have a polypeptide with SEQ ID NO: 4 and a light chain of SEQ ID NO: 8 and comprising a number of undisclosed deletions, substitutions or additions to the respective SEQ IDs. The antibody is also claimed as having at least one CDR (either of the heavy chain or light chain) (SEQ ID NOs 1-3 or 5-7) and comprising a number of undisclosed deletions, substitutions or additions to the respective SEQ IDs. The inflammatory cytokine may be any one of IFN- γ , TNF α , IL-1, and IL-6 and may also have an IL-10 production-inducing effect. The substance may be comprised in a pharmaceutical composition to be used in a method of inhibiting inflammatory cytokine production.

The rejection includes two issues which will be treated separately: the substances claimed and the second one relates to the antibodies per se.

In respect to the enablement for the substances claimed, the specification provides only a functional characteristic for the claimed substances, namely binding to CD61 and inhibiting cytokine production. Except to the structural limitations provided for antibody #33, there is no structure presented for the other substances that would lead a person of ordinary skill in the art to recognize the potential of that substance to have the properties claimed in the instant Application.

The prior art is aware of polypeptides and small molecules that bind to CD61 but not necessarily affecting the inflammatory cytokine production (e.g., fibrinogen, fibronectin, fibronectin-derived polypeptides (D-11-T), von Willebrand's factor, Vitronectin, Tsp (Thrombospondin), osteopontin and Bsp1 (bone sialoprotein 1),

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BIBU52 non-peptidic molecule) (Ginsberg et al., U.S. Pat. 5,773,574; Ashkar S., US20020058336; Guth et al., J. Cardiovascular Pharmacol., 30, 261-272, 1997). However, there is no indication in the art at the time that the invention was made that any DNA or RNA would bind to CD61 and modulate the inflammatory cytokine production.

As presented above, the specification does not provide any working examples for the "substances" claimed except for the antibody Ab#33 and no guidance is provided for the make and use of deoxyribonucleic acids, ribonucleic acids, proteins, peptides, and low-molecular substances or derivatives in a manner commensurate with full scope of the claims. It is submitted that an excessively large amount of experimentation is needed to make the "substances" (absent a nexus between structure and function) and to test for the desired function of binding and inhibit the production of inflammatory cytokine as well as for using them in a method of inhibiting the production of the cytokines mentioned above).

Due to the large quantity of experimentation necessary to generate the undisclosed number of substances and derivatives recited in the claims and possibly screen the same for activity; the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity; the absence of working examples directed to same; the complex nature of the invention; the state of the prior art which establishes the unpredictability of the effects of the substances with regard to the modulation of cytokine production; and the breadth of the claims which fail

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to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and use the claimed invention in its full scope.

Regarding the second aspect, scope of enablement for the antibodies, the rejection relates to obtaining an antibody that is defined by one CDR only or has a number of undisclosed deletions, substitutions or additions to CDRs or to the variable heavy or light chains. As presented supra such molecules lack adequate written description. In order to be functional, such a molecule has to be an antibody which has necessary requirements (which are attained by Antibody #33 of the instant Application). The art at the time that the invention was made describes a screening process using a mouse V_L and a human V_H library with CDR3 and FR4 retained from the mouse V_H . After obtaining antibodies, the V_H was screened against a human V_L library to obtain antibodies that bound antigen (Klimka et al., British Journal of Cancer 83: 252-260, 2000). Another screening process is described as using the entire mouse heavy chain and a human light chain library. After obtaining antibodies, one V_L was combined with a human V_H library with the CDR3 of the mouse retained. Antibodies capable of binding antigen were obtained (Beiboer et al., J. Mol. Biol. 296:833, 2000). However, the specification does not disclose that the antibody containing a CDR of the V_H chain alone can be transferred to just any framework and paired with just any V_L chain and retain antigen binding. The specification does not provide any examples to support that a CDR of the V_H or V_L is solely responsible for antigen binding and this another essential step missing since it was known in the art that a number of residues outside the CDRs make antigen contacts and residues in the CDRs are important for backbone conformations

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(MacCallum et al., J. Mol. Biol. 262: 732-745, 1996). Thus, summarizing, the prior art does not show that one CDR is universally solely responsible for antigen binding. The prior art does not show screening for antibodies by just defining one CDR. The methods rely on using an entire V_H or V_L and screening random complimentary chains. The prior art does not support a definition of an antibody structure solely by defining a CDR sequence of a V_H or V_L .

The working examples disclosed in the specification provide enablement only for the Ab#33 but not for other antibodies claimed. Therefore, it is considered that, because of the large quantity of experimentation necessary to generate the unknown number of potentially binding molecules recited in the claims and possibly screen the same for activity; the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity; the absence of working examples directed to same; the state of the prior art which establishes the unpredictability regarding obtaining antibodies with desired properties based on one CDR only; undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6, and 10-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Specifically, the independent claims 1 and 10-13 lack adequate written description so that the metes and bounds of the claims could not be determined. The dependent claims are rejected for depending on a rejected claim. In addition, claim 6 is indefinite because "An inhibitor" is not a composition. Therefore, there is only one ingredient. The claim should be amended to recite "A composition comprising..."

Claim 16 is also rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the active steps in the method as well as the objects upon which the method is performed.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

9. Claims 1-6, 14 - 16 are rejected under 35 U.S.C. 102(e) as being anticipated by Mills et al. (US Pub. 20070190078).

Mills et al. teach a filamentous haemagglutinin (FHA) or a derivative or mutant or fragment or variant or peptide thereof. The virulence factor, filamentous haemagglutinin (FHA) from *B. pertussis*, is capable of inhibiting LPS-driven IL-12 production by macrophages, IL-12 and IFN- γ production in a murine model of septic shock. FHA binds to leukocyte response integrin ($\alpha_v\beta_3$, CD61). FHA interacts directly with dendritic cells (DC) to induce IL-10 and inhibit LPS-induced IL-12 and inflammatory chemokine production ([0004]). Also taught are pharmaceutical compositions and methods of modulating an immune response in a mammal to a selected antigen, the method comprises administering to a mammal a therapeutic amount of an agent comprising FHA (which binds CD61) or a derivative or mutant or fragment or variant or peptide thereof or products of cells activated by these materials or administering a therapeutic amount of an agent comprising FHA or derivative or mutant or fragment or variant or peptide thereof ([0159]).

Thus, Mills et al. anticipates the claims of the instant Application.

10. Claims 1-6 and 10-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Reiner et al. (*J. Immunol. Meth.*, 184, 153-162, 1995).

Reiner et al. describe the use of the monoclonal antibody raised against the SZ21 epitope of the CD61 (also known at that time as GPIIIa) (right col., lines 10-16).

The antibody is the same as the antibody # IM2116 sold commercially by Beckman-Coulter Inc. as early as 03/02/2001 (see the evidentiary attachments IM2116-2.pdf and IM2116AA_SZ21.pdf) and was also used by the Applicant besides the claimed Ab#33. According to the Specification (Example 4) the Ab#33 of the instant

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Application and the anti –CD61 Beckman–Coulter Inc. bind different epitopes but they have the same effects and the Specification concludes that the epitope is not critical for the effect of the antibody as long as the antibody binds to the CD61 antigen.

Therefore, the antibody used by Reiner et al. anticipates claims 1-6 of the Instant Application.

11. Claims 1-6 and 10-16 rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Dingivan C. (U.S. Pub. No.: 20030044406).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Dingivan C. teaches methods of preventing, treating or ameliorating an autoimmune or inflammatory disorder or one or more symptoms thereof utilizing combinatorial therapy, by combining administering to a subject in need thereof one or more CD2 antagonists and at least one other therapeutic agent (abstract). The antibodies used encompass antibodies or antigen-binding fragments thereof that immunospecifically bind to integrin $\alpha_v\beta_3$ recombinantly fused or chemically conjugated (including both covalently and non-covalently conjugations) to a heterologous polypeptide to generate fusion proteins ([0374]). The β_3 component of the integrin mentioned is the CD61 antigen claimed. Since the Office does not have the facilities for examining and comparing applicants' Ab#33 with the antibodies of the prior art, the

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burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same material structural and functional characteristics of the claimed protein). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.). It is noted that since applicants stated that any binder of CD61 will have the anti inflammatory effects claimed in the instant Application, that any argument that Dingivan C, was somehow less enabled than applicants will be examined very critically.

12. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

- Berchtold et al. (WO/98/55619 -English version CA2293693) teaches Fab fragments which exhibit specific binding to GPIIIa (p.3, lines 1-9).

Conclusion

13. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ELLY-GERALD STOICA whose telephone number is (571)272-9941. The examiner can normally be reached on 8:30-17:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on (571) 272-0939. The fax phone

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number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lorraine Spector/ Ph.D.

Primary Examiner, Art Unit 1647